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Maternal Uniparental Heterodisomy for Chromosome 16: Case Report

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A patient with uniparental heterodisomy for chromosome 16 presented initially at prenatal diagnosis with a karyotype of 47, XX + 16 on chorionic villus sampling at 11 weeks gestation. The pregnancy was proceeding normally and follow up amniocentesis showed a normal female karyotype. At birth, the child was healthy, but had intrauterine growth retardation. She had unilateral talipes equinovarus and unilateral renal agenesis. Her growth had improved to within the normal range by age three years. On examination, she has epicanthic folds, a flat midface and almond shaped eyes. While these characteristics are not frankly abnormal, they are significantly different from other relatives in her family. Am. J. Med. Genet. 70:387–390, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: uniparental disomy; chromosome 16; facial anomalies; renal agenesis

INTRODUCTION

Uniparental disomy (UPD) is a recently recognized phenomenon which can give rise to congenital disorders in humans by mechanisms other than classical Mendelian genetics. The main mechanisms identified so far are imprinting anomalies as in the Prader-Willi syndrome [Cassidy et al., 1992], or homozygosity of the chromosome homologues [Spotila et al., 1992; Spence et al., 1988]. The most consistent findings of UPD described so far have been intrauterine growth retardation (IUGR) and spontaneous abortion [Kalousek et al., 1991, 1992, 1993; Kennerknecht et al., 1990]. Many cases of UPD appear to be completely normal apart from IUGR.

Cases of UPD may be important to basic scientists for two reasons. Firstly, they may provide insight into imprinted areas of the human genome. Secondly, malsegregation with homozygosity over a defined stretch of a chromosome may help localize new genes [Woodage et al., 1994].

Perhaps the most common mechanism for the development of UPD suggested to date has been malsegregation of chromosomes in a trisomic conception [Kalousek, 1993, 1994].

We describe a patient with UPD of chromosome 16 developing from trisomy 16 detected prenatally by chorionic villus sampling.

Clinical Report

This is the second child of a healthy Caucasian couple. The mother was 42 years old and the father 36 years old at the time of conception. There was one older normal sibling.

Chorionic villus sampling was performed at 11 week's gestation for advanced maternal age. On long term culture, all 20 colonies were found to have the karyotype 47, XX + 16. However, the pregnancy continued normally and on ultrasound examination no abnormalities of growth or structures were seen. Confined placental mosaicism was suspected and amniocentesis at 14 week's gestation showed a fetal karyotype of 46,XX in 17 colonies.

During the third trimester, hypertension without proteinuria was noted.

At 33 week's gestation, while visiting relatives in another city, the mother suddenly developed an antepartum hemorrhage and was admitted for investigation. Placenta praevia was diagnosed and emergency Cesarean section was carried out for fetal distress. The baby required resuscitation and was ventilated for one day for respiratory distress.

The baby weighed 1,620 g at birth. She was 42 cm long and had an OFC of 29 cm (all measurements below the 3rd centile). Physical examination at birth showed right talipes equinovarus. Ultrasound examination of the abdomen showed left renal agenesis. Chromosome studies were repeated on lymphocytes and confirmed a normal female karyotype.

At age 1 year, the patient was referred to the genetics clinic for assessment. The infant weighed 7,700g (below 5th centile) and was 70 cm long (5th centile).

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The OFC was 45.5 cm (normal for age). The body was proportionate apart from a large appearing head. There were no physical abnormalities on examination, but the eye shape was different from the rest of the family. There were mild epicanthic folds, an almond shape to the palpebral fissures and a slightly flatter facial profile (Fig. 1). Talipes equinovarus in the right foot had been surgically corrected.

Development was normal at three years of age. Full psychomotor assessment showed normal development on the Bayley scales. There had been no significant medical complaints. Physical growth showed that the weight had increased to 1,150g (25th centile), the height was 85 cm (just above the 10th centile) and the OFC was 48 cm (mean). The facial appearance was as previously observed but less distinctive with age. DNA was extracted from peripheral blood of the parents and the proband.

Molecular Studies

The DNA was digested with PvuII and following Southern blotting was probed with P32-labeled D16S85 (the 5′HVR from the alpha-globin region of chromosome 16). This showed both maternal alleles in the child and neither paternal allele (maternal heterodisomy). Subsequently, several other chromosome 16 microsatellite polymorphisms, including markers from the ABI PRISM chromosome 16 specific panel (Applied Biosystems Inc.) [Weissenbach et al., 1992; Gyapay et al., 1994] were analyzed on an ABI 377 automated sequencer. Inheritance of markers for D16S405, D16S407, and D16S520 were consistent with maternal uniparental disomy, and at two of these loci paternal contributions could be excluded (Table I). Because fairly distal markers on both 16p and 16q showed no paternal contributions, we believe that maternal uniparental heterodisomy can be assumed for the whole chromosome. The child is heterozygous from D16S520 to D16S393, but homozygous (like the mother) at the 16q telomeric marker D16S520. Most of the two chromosomes 16 in the child appear to be derived from the two copies in her mother prior to the non-disjunction in meiosis I. Only the most distal regions of 16q could be reduced to homozygosity as described by Bridge [1994].

DISCUSSION

Uniparental disomy is now a well-described phenomenon. The phenotypes arising from UPD depend upon which chromosomes are involved. UPD for imprinted areas (for example, chromosome 15) may give rise to recognizable syndromes (Prader-Willi syndrome, Nichols et al., [1989]; Angelman syndrome, Malcolm et al., [1991]). Paternal and maternal UPD for chromosome 14 has been associated with abnormal phenotypes [Wang et al., 1991; Temple et al., 1991; Healey et al., 1994]. Maternal UPD for chromosomes 13, 21 and

Fig. 1. Appearance of the proband at 3 years of age. Note the mild epicanthic folds and mild midfacial hypoplasia.

TABLE I. Inheritance of Chromosome 16 Markers

Locus	Location	Father	Child	Mother	Method[a]	Conclusion
D16S85	6p13.3	A,B	C,D	C,D	S	Maternal heterodisomy
D16S283	16p13.3	A,B	B,B	B,B	M	
D16S423	16p13.3	136,142	118,136	118,136	F,M	
D16S407	16p13.2	269,281	267,277	267,277	F	Maternal heterodisomy
D16S405	16p13.1	133,133	133,135	133,135	F	
D16S503	16q21	293,303	293,299	293,299	F	
D16S393	16q24.1	140,152	150,158	150,158	M	Maternal heterodisomy
D16S520	16q24.1-qter	153,157	155,155	155,155	F	Maternal UPD

[a]S, Southern blotting; M, radioactive microsatellite; F, fluorescent microsatellite.

22 has been described with no phenotypic abnormalities [Slater et al., 1994; Blouin et al., 1993; Schinzel et al., 1994]. Growth failure has been described with UPD for chromosome 7 [Langlois et al., 1995]. Neonatal diabetes has been described for Paternal UPD 6 [Temple et al., 1995]. One child has been described with hemifacial microsomia, but this child was chimeric for a parthogenetic cell line (in blood) and for a diploid diparental cell line in fibroblasts [Strain et al., 1995]. In UPD 16, single case reports of imperforate anus, talipes equinovarus [Kalousek et al., 1993] and unilateral renal agenesis (this case) have also been described. Hall [1990] has suggested that part of chromosome 16 may be imprinted based on mouse studies.

Non-disjunction appears to have occurred in meiosis 1 in our patient. If nondisjunction had occurred in meiosis II (after crossing over), there would have been regions of chromosomal homozygosity, increasing the risk of autosomal recessive disorders. There is no support to suggest that the unilateral renal agenesis in this patient is caused by an autosomal recessive gene.

Chorionic villus sampling frequently provides the first indication of the possibility of UPD. A discrepancy between fetal and placental karyotypes has been observed frequently in the past and has been called confined placental mosaicism (CPM) [Kalousek and Dill, 1993]. CPM is thought to occur in approximately 1-2% of all pregnancies [Simoni et al., 1985: Kalousek et al., 1993]. The main clinical association has been with intrauterine growth retardation [Kalousek et al., 1991; Wolstenholme et al., 1994; Williams et al., 1992; Kennerknecht and Terinde, 1990; Hashish et al., 1989; Kalousek et al., 1993; Bennet et al., 1992; Dwoornicsak et al., 1992; Garber et al., 1994] and spontaneous abortion [Kalousek et al., 1992].

Differences in physical appearance in UPD 16 patients have not previously received comment. Our patient was not abnormal, but her appearance was different from other relatives in her family, even taking into account her smaller size. We do not know if this is consistent for UPD 16 patients as complete clinical reports on these patients are not available.

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